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Multimodal Hypersensitivity Derived from Quantitative Sensory Testing Predicts Pelvic Pain Outcome: an Observational Cohort Study

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Abstract

Multimodal hypersensitivity (MMH)—greater sensitivity across multiple sensory modalities (e.g., light, sound, temperature, pressure)—is associated with the development of chronic pain. However, previous MMH studies are restricted given their reliance on self-report questionnaires, narrow use of multimodal sensory testing, or limited follow-up. We conducted multimodal sensory testing on an observational cohort of 200 reproductive-age women including those at elevated risk for chronic pelvic pain conditions and pain-free controls. Multimodal sensory testing included visual, auditory, bodily pressure, pelvic pressure, thermal, and bladder pain testing. Self-reported pelvic pain was examined over four years. A principal component analysis of sensory testing measures resulted in three orthogonal factors that explained 43% of the variance: MMH, pressure pain stimulus-response, and bladder hypersensitivity. The MMH and bladder hypersensitivity factors correlated with baseline self-reported menstrual pain, genitourinary symptoms, depression, anxiety, and health. Over time, MMH increasingly predicted pelvic pain and was the only component to predict outcome four years later, even when adjusted for baseline pelvic pain. MMH was a better predictor of pelvic pain outcome than a questionnaire-based assessment of generalized sensory sensitivity. These results suggest that MMH's overarching neural mechanisms convey more substantial long-term risk for pelvic pain than variation in individual sensory modalities. Further research on the modifiability of MMH could inform future treatment developments in chronic pain.

Keywords

Multimodal hypersensitivity; sensory testing; pelvic pain

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Multimodal hypersensitivity (MMH), a hallmark feature of chronic pain conditions [23,29,34,43,53,78,95], is associated with the development of chronic pain [8,38] and serves as a determinant of treatment response [35,45]. MMH is increased sensitivity across multiple sensory modalities (e.g., light, sound, temperature, pressure) common in functional or chronic pain conditions [5,29,85]. Individuals with chronic pelvic pain conditions, like irritable bowel syndrome and bladder pain syndrome, similarly exhibit degrees of MMH despite not having any outward pelvic pathology (e.g., infection, endometriosis, etc.) [58,85]. Previous studies have attempted to quantify MMH [7,17,39,63,92], its stability over time [85], and its relationship to chronic pain severity and outcome [46,66,67,86]. Our understanding of MMH is limited given these investigations often relied on subjective self-report questionnaires (e.g., generalized sensory sensitivity [85]), inadequately assessed MMH by using unidimensional quantitative sensory testing (QST), or lacked long-term follow-up. Despite the ubiquitous use of QST to study pain conditions [89], we lack a full picture of how different QST methods relate to each other and predict changes in pelvic pain symptomatology [41,66]. A synergistic approach encompassing multiple modalities of QST with longitudinal symptom assessment could improve our understanding of MMH and further quantify an individual's susceptibility to developing chronic pain.

Therefore, we performed secondary analyses on a four-year longitudinal cohort of young reproductive age women that had multimodal sensory testing performed at baseline (CRAMPP: Chronic Pain Risk Associated with Menstrual Pelvic Pain; NCT02214550). Because menstrual pain is among the leading risk factors for chronic pelvic pain [62,100], we focused on recruitment of women with significant menstrual pain. We also included pain-free controls and a subset of women with chronic pelvic pain to provide a full range of sensory profiles for analysis. CRAMPP's multimodal sensory testing battery included provocation with pressure, cold, and audio/visual stimuli, temporal summation (a measure of spinal wind-up), conditioned pain modulation (a metric of descending inhibition), and bladder distension (a measure of visceral sensitivity). Analysis of CRAMPP's baseline data revealed that individuals with dysmenorrhea and bladder pain hypersensitivity have impaired conditioned pain modulation, increased sensitivity to pressure and thermal stimuli (e.g., cold) [51], and visual provocation [59], even without any formal chronic pain diagnoses. However, we have not explored whether these sensory sensitivities were unified (i.e., MMH) and predicted long-term pelvic pain outcome. Therefore, we analyzed the measures obtained from sensory testing in two ways. We combined our multimodal sensory testing panel measures into three *a priori* defined sensory testing composites: traditional QST, non-invasive bladder distension (i.e., provoked visceral sensitivity), and supraspinal audio/visual sensitivity. Their ability to predict longitudinal pelvic pain outcome was compared to sensory testing components that were instead derived from principal component analysis (PCA). We hypothesized that the PCA would produce an MMH component that would predict long-term pelvic pain outcome and outperform our *a priori* composites of sensory testing.

Methods

Participants

A total of 354 participants were enrolled in CRAMPP between August 2014 and December 2018 (see Figure 1). Participants were recruited by public advertising and flyers in Evanston, Illinois and the surrounding communities. The severity of menstrual pain was confirmed with internet-based prospective symptom diaries for 1–2 months prior to enrollment [51].

Enrolled participants included women with low menstrual pain (<3 on a 0–10 Numerical Rating Scale [NRS]; 0 = no pain; 10 = worst pain imaginable) or moderate to severe menstrual pain (≥5 on a 0–10 NRS) but no other chronic pain. We also included participants diagnosed with bladder pain syndrome (BPS), and participants diagnosed with a non-pelvic chronic pain condition (general pain ≥5 on a 0–10 NRS for more than three consecutive months). BPS participants were required to meet American Urological Association diagnostic criteria, and report bladder pain ≥3 on a 0–10 NRS for more than 3 consecutive months [42].

Participants were excluded for the presence of active pelvic or abdominal malignancies, absence of regular menses (except the chronic pain without BPS group), active genitourinary infection in the last four weeks, inability to read or comprehend the informed consent in English, refusal to undergo pelvic examination/testing, hypertension, or refusal to withdraw from oral contraceptives for two months prior to the study visit. All participants provided informed consent and followed protocols approved by NorthShore University HealthSystem's Institutional Review Board (EH13–094). Participants were monetarily compensated for their time.

From the 354 participants, n=154 were excluded for the following reasons: 52 participants were missing one or more data points from QST (e.g., declined participation in task(s), equipment malfunction, migraine sensitivity precluded participation in visual stimulation, etc.) and one participant was under the influence of recreational or illicit substances during the testing appointment. Additionally, 25 participants were lost to follow-up, 16 participants withdrew from the study, and 60 participants were disqualified (e.g., over-recruited dysmenorrhea without bladder pain, started oral contraceptives, or were unable to complete protocol). Ultimately, a total of 200 participants had complete QST data from their baseline assessment visit.

Participants completed annual questionnaires following their baseline visit for up to five years. Annual questionnaires were a reduced version of what was asked at their screen and baseline assessment visits and were used to assess pelvic pain outcome. Because the collection of year five annual questionnaires was incomplete at the time of analysis, we included here completed annual questionnaires until year four. Demographic variables of interest are presented in Table 1.

From the 200 participants with complete QST data, 22 were randomized into a 12-month clinical trial that evaluated the efficacy of cyclical (n=4) and continuous (n=12) oral contraceptive pills (OCPs) for treating menstrual and bladder pain compared to a control

group that did not take OCPs (n=6). QST was administered by research staff unaware of participant group assignment or history. Because of the low adherence to OCP use and small comparative sample sizes, we did not consider participants' enrollment in the clinical trial as exclusionary from our analyses of subsequent annual questionnaires. In addition, multimodal sensory testing was performed on all participants before beginning the use of OCPs, so analyses on internal relationships of MMH on longitudinal outcome were not expected to be confounded by OCP use.

Procedure

Eligible participants that were enrolled in the study first participated in a screen visit and then a second baseline assessment visit at Evanston Hospital (Evanston, IL). During the baseline visit, performed in the midluteal (pain-free) phase of the menstrual cycle, participants completed a panel of medical history and psychosocial questionnaires. Participants next underwent a multimodal sensory testing panel that included mechanosensation, cold pressor, visceral provocation, conditioned pain modulation (CPM), temporal summation (TS), and auditory/visual stimulation. All sensory testing measures and self-report questionnaires are detailed below.

Bladder Filling Test—We have developed a non-invasive bladder filling task [90] to characterize visceral hypersensitivity observed across CPP conditions like bladder pain syndrome and irritable bowel syndrome [6,30,57]. This task has been validated in participants with bladder pain syndrome and chronic pelvic pain [91]. Notably, even in participants without bladder pain conditions, elevated pain during this task was associated with more frequent report of daily bladder symptoms [49]. After voiding their bladder, participants ingested 20 fluid ounces of water. They rated their bladder pain and urgency on a 0–100 VAS across four time points: baseline (BL), first sensation (FS) of bladder filling, first urge (FU) which is the usual desire to void their bladder, and maximum tolerance (MT) of bladder filling (corresponding to widely used cystometric sensory thresholds) [48]. After reaching maximum tolerance (or 2 hours) and voiding their bladder, participants rated their perceived bladder pain on 0–100 VAS according to four McGill pain questionnaire descriptors to potentially differentiate Aδ from C fiber pain components: sharp, pressing, dull, and prickling [10]. In sum, 12 measures from the bladder task were included in this analysis (i.e., four provoked bladder pain ratings and four bladder urgency ratings across the time points, and four McGill descriptor ratings at completion).

Pressure Pain Thresholds (PPTs)—We examined PPTs transvaginally and externally because local alterations in myofascial pelvic sensitivity [50] and widespread alterations in bodily sensitivity are thought to underlie centralized pain [37]. We determined participants' PPTs using a digital algometer (Wagner Instruments, Greenwich, CT) with a 1-cm^2 rubber tip driven at a ramp rate of 4 Newtons (N)/sec at three fibromyalgia tender point sites [97]—right trapezius, the right medial knee fat pad, and the right greater trochanter (hip)—and the forehead. Vaginal PPTs were measured using a finger mounted 1 cm^2 diameter force-sensing resistor (Trossen Robotics, Downers Grove, IL) at a ramp rate of 0.5 N/sec at four vaginal sites: right (5 o'clock position) and left iliococcygeus (7 o'clock), anteriorly against the bladder (12 o'clock), and posteriorly against the anorectal raphe (6 o'clock). Body and

vaginal PPT procedures utilized software that guided stimulus application and resulted in high (α > .89) inter- and intra-examiner reliability [51]. After each set of PPTs, participants were asked to rate their pain on a 0–10 NRS at each site. These after-pain ratings were adjusted for baseline pain ratings recorded before PPT procedures. We previously established that PPTs and after-pain represent two different components of sensation contributing to MMH [50]. PPTs represent the average force from two independent trials separated by a 2 minute break period. These averaged PPTs were multiplied by −1 so that a greater value indicates increased sensitivity. In total, 16 PPT measures were included in the planned PCA: eight PPTs (four body and four vaginal sites) and eight after-pain ratings (four body and four vaginal sites).

Conditioned Pain Modulation (CPM)—We included CPM in our QST panel because prior studies have demonstrated that CPM predicts pain outcome [98,99]. CPM efficiency is thought to be a metric of descending inhibition as tested by “pain inhibits pain” paradigms [70]. We assessed participants’ CPM by repeat PPT testing of the left medial knee fat pad before and after ice water immersion of the contralateral hand. After an initial PPT measurement, participants waited two minutes before submerging their right hand up to their wrist into a circulating water bath maintained at 0–6°C. After 10 seconds of submersion, participants rated their hand/cold pain on a 0–10 NRS. After 20 seconds of submersion, a repeat PPT measure was taken from the left medial knee fat pad, after which participants were allowed to remove their hand from the cold-water bath. CPM was calculated by subtracting the PPT force (in Newtons) taken before the water bath from the PPT taken after the water bath (i.e., CPM =After-Before). CPM values were then multiplied by −1 so that a greater number denoted reduced/inefficient CPM (i.e., increased impairment) before including results in the PCA. Additionally, cold pain ratings were adjusted for the water temperature by extracting the residuals from a linear model predicting cold pain as a function of water temperature. In total, two measures from CPM testing were included into the PCA: one CPM score and one cold pain rating adjusted for water temperature.

Temporal Summation (TS)—Increased response to repeated application of noxious stimuli (i.e., wind-up pain) is thought to reflect a unique component of spinally mediated sensitization that may be associated with increased risk of chronic pain [19,71,88]. Therefore, we measured TS using a commonly used strategy: 10 pressure pulses delivered to the right medial knee fat pad using the same body PPT algometer as described above [19]. Each pulse was delivered at a ramp rate of 4 N/sec with 1 second breaks between pulses using a software-based metronome to guide application. Each pulse was applied until the initial threshold for a pain rating of one was reached. Participants rated their baseline pain at the application site on a 0–10 NRS following each pulse. The TS task ended when participants reached a pain rating ≥ six or after the tenth trial. Each participant’s baseline pain was subtracted from their pain ratings collected after each pulse. A total of three TS measures were entered into the PCA: the average pain experienced during TS, the rate of change in pain ratings as a function of trial (i.e., slope), and the maximum TS trial experienced. The maximum TS trial was multiplied by −1 so that greater values indicated increased sensitivity (i.e., fewer trials allowed due to reaching a pain rating of six).

Visual Stimulation—Investigations of MMH are well served to include additional sensory modalities, such as vision, given that light hypersensitivity is commonly reported in conditions with generalized sensory hypersensitivity, like fibromyalgia and migraine [32,45,65]. We assessed participants' visual unpleasantness sensitivity by presenting a periodic pattern-reversal blue/yellow checkerboard stimulus alternating at 25 Hz for 20 seconds across five blocks. Each block contained a single maximal brightness intensity (1, 30, 60, 90, or 120 lux), and block order was randomized across participants. After each block, participants rated stimulus unpleasantness using the Gracely Box Scale which lists the numbers 0 to 20 next to a set of verbal anchors [36]. A total of two visual sensitivity measures were entered into the PCA: the average visual unpleasantness rating across the blocks, and the rate of change in visual unpleasantness as a function of brightness intensity [59].

Auditory Stimulation—Auditory stimulation assessed an additional sensory modality with reported hypersensitivities in functional pain syndromes [53,64,95]. Prior to measuring the participants' auditory unpleasantness sensitivity, a program first verified that participants maintained less than 20 dB hearing loss (250–8000 Hz) [75] to equate hearing ability. Next, we presented a series of auditory steady state 80Hz [26] volume modulated tones (1200 and 1350Hz) in random order of intensity (15, 30 45, or 60 dB) delivered via ground-isolated optimally flat frequency response pneumatic insert earphones (Etymotic, Elk Grove Village, IL). After each 20 second stimulus, the participant rated her perceived unpleasantness on the Gracely Box Scale as described above. A total of two auditory sensitivity measures were entered into the PCA: the average auditory unpleasantness rating across the blocks, and the rate of change in auditory unpleasantness as a function of loudness intensity (i.e., slope).

We recorded participants' scalp electroencephalography (EEG) during visual and auditory sensitivity tasks. Given the behavioral focus of this investigation, these EEG data were out of scope and not included in the present investigation. EEG data from the visual task are published elsewhere [59].

Self-Report Questionnaires—In the health history profile, we administered several validated self-report questionnaires that assessed various aspects of pelvic pain and associated symptoms. Bladder symptom severity was assessed via the Interstitial Cystitis Symptom Index (ICSI) and Problem Index (ICPI) [72]. The Genitourinary Pain Index (GUPI) provided a complementary assessment of these urogenital symptoms [20]. The Complex Medical Symptoms Inventory (CMSI) was used to assess functional symptom burdens that occurred for at least three months in the past year and at any time in the participants' lifetime [96]. Somatic symptoms were assessed using the Brief Symptom Inventory (BSI) [25]. We assessed several health domains from the NIH Patient Reported Outcomes Measurement System (PROMIS) [16], including anxiety (short form 8a), depression (8b), pain interference (6), pain behavior (7), global physical health (4), and global mental health (4). Specifically, PROMIS raw short form scores were analyzed. Menstrual pain is associated with non-cyclic pelvic pain [93] and non-pelvic pain hypersensitivity [51,54,73,74], suggesting that menstrual pain may be a risk factor for developing chronic pain [54,73]. Therefore, we assessed participants' menstrual pain on a

0–100 VAS on the worst day of their period over the past three months in the absence of pain relievers (e.g., non-steroidal anti-inflammatory drugs [NSAIDs], acetaminophen, etc.)

Pelvic Pain Outcome

Participants completed annual questionnaires virtually by email in REDCap for up to four years. As part of this questionnaire, participants rated their average feeling of 1) menstrual and non-menstrual pelvic pain, 2) pain with urination, and 3) pain with bowel movements during the past week using a 0–100 VAS (0=no pain; 100=worst pain imaginable). VAS scales are more sensitive to changes than descriptive word-based scales [87] and have linear properties amenable to averaging [68]. Also, these three questions were highly collinear at the baseline assessment: 1 vs. 2, $r(198) = .61$ 95% confidence interval (CI) [.51, .69], $p < .001$; 1 vs. 3, $r(198) = .56$ [.45, .65], $p < .001$; and 2 vs. 3, $r(198) = .66$ [.57, .73], $p < .001$. Therefore, we averaged these three questions to create a composite pelvic pain outcome variable. Similar composite pain recall variables formed by averaging have demonstrated high validity and reliability comparable to daily diary pain ratings [56].

QST, Bladder Test, and Audio/Visual Predictor Composite Variables

To evaluate the ability of different sensory tests to predict pelvic pain outcome, we combined the 40 measures from the multimodal sensory testing panel into three composite variables using summed Z-scores: traditional QST measures, bladder test measures, and audio/visual stimulation. The QST composite comprised 25 measures including PPTs (i.e., thresholds, after pain, and descriptors), TS, CPM, and cold pain. The bladder test composite comprised 11 measures from the bladder test, including pain, urgency and descriptors. The audio/visual sensitivity composite comprised 4 measures, including mean unpleasantness and slope of the stimulus-response function from the auditory and visual tests. Prior to calculating Z-scores, all measures maintained the same directionality such that greater values denoted increased pain/impairment/sensitivity. Final composites were mean centered for regression analyses.

Generalized Sensory Sensitivity Brief Scale

To examine the predictive ability of self-reported somatic symptoms, we utilized the Generalized Sensory Sensitivity Brief Scale (GSS Brief) [85]. The GSS Brief approximates GSS (developed using confirmatory factor analysis) that captures comorbid sensory hypersensitivity often present in chronic overlapping pain conditions. Participants indicate regions on a body map where they have experienced pain during the last week and endorse whether they had any of the following symptoms for at least three months in the past year: 1) dry mouth, 2) rapid heart rate, 3) problems with balance, 4) sensitivity to certain chemicals, such as perfumes, laundry detergents, gasoline, and others, 5) sensitivity to sound, and 6) frequent sensitivity to bright lights. The GSS Brief is a good approximation of GSS, and the GSS factor structure was recently replicated in the cohort used in this study [84].

Statistical Analyses

A formal power analysis was used to plan the broader clinical trial (NCT02214550). Because the present investigation was a secondary analysis, all participants' data were included if complete.

To assess how well baseline QST, bladder test, and audio/visual measures independently predicted future pelvic pain outcome, we performed four multiple regressions using self-report data from annual follow-up questionnaires. Pelvic pain outcome served as the dependent variable. The independent variables included the summed Z-scores (QST, bladder test, audio/visual sensitivity) defined above. We also included baseline pelvic pain outcome as a covariate. All independent variables were measures collected at the participants' baseline visit.

Additionally, we reduced the dimensionality of our sensory testing panel (40 measures/columns) using principal components analysis (PCA) [2]. All measures maintained the same directionality such that greater values denoted increased pain/impairment/sensitivity/etc. Each column was then Z-scored prior to decomposing the matrix via singular value decomposition [1].

Inferential statistics were performed using data resampling techniques [2,9]. Permutation testing for the PCA was conducted by creating null distributions for each principal component (PC) by shuffling each column's values without replacement and repeating the PCA for 2,000 iterations. Probability values for each PC were calculated by comparing our fixed-effects eigenvalues to their respective null distributions. Contributions were calculated by dividing each measure's squared factor score by the component eigenvalue [9]. Bootstrap samples were formed by selecting participants at random with replacement. Bootstrap distributions were formed by supplementary projecting the bootstrap samples onto the eigenspace generated from the fixed-effects analysis [9]. This procedure was repeated 2,000 times. Bootstrapping quantified each measure's loading stability/contribution importance using bootstrap ratios (BSRs). A BSR is the ratio between a measure's fixed-effect factor score (i.e., loading) and the standard deviation of its bootstrapped distribution. BSRs are interpreted like Student's t value. Therefore, significantly contributing measures have $|BSRs| > 1.96$ ($p < .05$).

To compare PCs with measures not included in their initial formulation, we calculated bootstrapped correlations between the row-wise (i.e., participant) factor scores and validated self-report questionnaires. To assess how well QST-based PCs predicted future pelvic pain outcome, we repeated the multiple regression procedure as described above except that pertinent PCs served as the independent variables instead of the three Z-scored measures.

A sensitivity analysis was performed to examine whether adjusting for prevalence rates of dysmenorrhea, bladder pain syndrome, and other types of chronic pain in the general population altered regression results. Keeping our sample size constant (n=200), participants were sampled with replacement according to the following prevalence rates [12,24,82]: 50% pain-free healthy controls (n=100), 40% moderate-severe dysmenorrhea (n=80), 5% bladder pain syndrome (n=10), 5% other chronic pain (n=10). Regression analyses were recomputed using these bootstrapped data samples. This procedure was repeated for 2,000 iterations. Mean regression estimates and effect sizes were then compared to original unadjusted values.

We conducted post hoc model comparison analyses to assess the relative performance of PCs over *a priori* defined sensory testing composites (summed Z-scores) in predicting future pelvic pain. Given the multicollinearity between PCs and the composites, we compared the Akaike and Bayesian information criterion (AIC and BIC, respectively) values between two models estimated separately at each year of follow-up in accordance with previously published guidelines [18]. Evidence ratios for the best model versus a comparator model were calculated as $\exp\left\{-\left(\frac{1}{2}\right)\Delta\right\}$ where Δ is the change in AIC between models [see 18].

Analyses were performed in R (4.1.0) within RStudio (1.4.1106) using the following packages: fixed- and random-effects PCA were performed using *ExPosition* [9], bootstrapped correlations were computed using *psych* [76], effect sizes were calculated using *effectsize* [11], data processing and figures were generated using *tidyverse* packages [94], color palettes were inspired by *RColorBrewer* [69] and *ghibli* [52]. All code used to process, analyze, and visualize the data in this manuscript is available on GitHub (https://github.com/mkmiecik14/mmh), and data are available on Open Science Framework (https://doi.org/10.17605/OSF.IO/27KY9).

Results

QST and Visceral Sensitivity Modestly Predict Pelvic Pain Outcome

Distributions of predictor variables are visualized in Figure 2A (see Table 2 and Table 3 for complete sensory testing data). Median pelvic pain outcome across the four-year follow up was stable and many participants reported moderate pelvic pain (see Figure 2B left panel). Cross-sectional relationships between sensory tests and baseline pelvic pain demonstrated that sensitivities across the QST, bladder test, or audio/visual composites were associated with worse baseline pelvic pain (see Figure 2B right panel).

Multiple regressions were used to assess how well QST, bladder test, and audio/visual testing predicted pelvic pain outcome on annual questionnaires administered up to four years following the baseline visit (see Table 4). We accounted for baseline pelvic pain by including it as a covariate (see Table S1 for descriptive statistics). Baseline pelvic pain was the strongest predictor of year 1 pelvic pain, but steadily declined over time (see Figure 2C left panel). The bladder test and QST predicted pelvic pain at years 3 and 4, respectively. Audio/visual testing did not predict outcome at any year. After adjusting for population-based prevalence rates of patient groups, baseline pelvic pain was a stronger predictor of year 4 pelvic pain outcome (see Figure S1). Also, QST explained little to no variance in pelvic pain outcome at any year. Thus, overall baseline pelvic pain was a better predictor of future pelvic pain than QST, bladder test, and audio/visual composites during the first 3 years, but was not significant at year 4.

PCA Identifies Three Components Explaining Variability in Multimodal Sensory Testing

We determined the number of PCs underlying QST variability across the cohort by examining the scree plot (see Figure S2 and Table S2), permutation testing results, and loadings using geometrically plotted factor scores of QST measures [2]. Accordingly, we identified three components as interpretable. The first PC (PC1) explained 20.6% of the

variance (p = .0005), the second (PC2) 12.4% (p = .0005), and the third (PC3) 446 9.5% (p = .0005).

Factor score plots for the first three PCs are shown in Figure 3 (see Figure S3 for contributions and Figure S4 for bootstrapped significance of factor loadings). Given that all measures loaded positively on PC1, we interpret PC1 to represent *MMH* (i.e., increased sensitivity on one measure was associated with an increased sensitivity on another). Forehead, hip, knee, shoulder, and vaginal PPTs positively loaded on PC2, while their respective after-pain ratings were opposed on PC2. This factor is representative of a stimulus-response function of pressure and after-pain resulting from PPT testing, hereafter referred to as *PPT S-R* (PPT stimulus-response). In other words, participants with lower PPTs (i.e., less force, greater sensitivity) reported less after-pain ratings. PC3 depicted an opposing relationship between bladder task measures and PPTs (thresholds and after-pain ratings). Given that additional measures (e.g., visual mean) had weak loadings on PC2, *PPT-SR* may represent another complex integratory mechanism. However, the contribution of these additional measures steeply drops off (Figure S3). Given the orthogonality of PCs, PC3 captured *bladder pain hypersensitivity* that was distinct from PC1 (*MMH*). Hereafter, we distinguish our interpretations of the observed PCs from theoretical constructs by using italics for PC interpretations, e.g., *MMH* = PC1, and unitalicized text for theoretical constructs (e.g., MMH).

PCs Correlate with Baseline Self-Report Measures

Figure 4 depicts the bootstrapped correlations between row-wise factor scores (i.e., participants) of PCs and validated questionnaires of self-reported menstrual pain, genitourinary symptoms, depression, anxiety, and health (see Table S3 for descriptive statistics of self-report measures). *MMH* and *bladder hypersensitivity* correlated strongly with every measure included, while *PPT S-R* only weakly correlated with two standardized clinical questionnaires for bladder pain: the ICSI and GUPI. These widespread correlations observed across PCs 1 and 3, but not PC2, demonstrate that these two dimensions (*MMH* and *bladder pain hypersensitivity*) explain variability in participants' current pain- and health-related quality of life. Also, given the orthogonality of PCs, these results suggest the contribution of two mechanisms to explain patients' current pelvic pain health-related quality of life: 1) MMH and 2) bladder hypersensitivity.

PC1 (*MMH*) Predicts Longitudinal Pelvic Pain Outcome Four Years Later

Multiple regressions were used to assess how well the three obtained PCs (i.e., *MMH*, *PPT S-R*, and *bladder hypersensitivity*) predicted pelvic pain outcome on annual questionnaires administered up to four years following the baseline visit (see Table 5 for regression results). Distributions of the PCs are presented in Figure 2A. Similar to the self-report measures, baseline pelvic pain correlated with both *MMH* and *bladder hypersensitivity*, but not with *PPT-SR* (see Figure 2B right panel). PCs were orthogonal to each other (r=0).

Baseline pelvic pain was the strongest predictor of year 1 pelvic pain, but that association steadily decreased over time. In contrast, *MMH* increased in its predictability of pelvic pain outcome over time and predicted worse pelvic pain outcome continuously up to four

years later (see Figure 2C right panel). A 1*SD* increase in *MMH* at baseline predicted a .44*SD* increase, or nearly 6 VAS points, in pelvic pain ratings four years later. *PPT S-R* and *bladder pain hypersensitivity* did not predict outcome at any year. Adjusting for population-based prevalence rates of included diagnostic groups replicated the observed sample-wise regression results (see Figure S1). Thus, the positive association between *MMH* and pelvic pain was robust and differentiated participant four-year trajectories (see Figure 5). Additional analyses examining the effect of annual questionnaire attrition determined that longitudinal data were missing at random and did not selectively depend on recruited participant groups, pelvic pain outcome, nor predictor variables of interest (see the Supplementary Material section on attrition for details).

PC1 (*MMH*) Outperforms Composite and Questionnaire-based Measures of Sensory Sensitivity

We compared the added predictive value of *MMH* over sensory testing composites by comparing the AIC and BIC values between two models estimated separately at each year of follow-up: 1) the MMH model regressed pelvic pain outcome on *MMH* and 2) the composite model regressed pelvic pain outcome on the QST, bladder test, and audio/visual summated Z-scored composite variables. Baseline pelvic pain served as a covariate in both models. Across all four follow-up years, the MMH model was the best model with the lowest AIC and BIC values. The strength of the evidence (i.e., evidence ratio) for the MMH model over the composite model (i.e., *n*x denotes evidence is *n* times stronger for the MMH than composite model) using the more conservative AIC was 7.28x at year 1 (ΔAIC = 3.97, ΔBIC = 9.90), 9.50x at year 2 (ΔAIC = 4.50, 508 ΔBIC = 10.2), 1.73x at year 3 (ΔAIC = 1.10, ΔBIC = 6.25), and 5.58x at year 4 (ΔAIC = 3.44, ΔBIC = 8.37) [18]. These results suggest a preference for the simple and more parsimonious MMH model in predicting pelvic pain outcome over the composite model.

To compare *MMH* to the GSS Brief—a questionnaire-based measurement of increased sensory and diffuse pain sensitivity—we examined their correlations and compared their performance in predicting pelvic pain using multiple regression. Zero-order Pearson correlations demonstrated a strong positive association between baseline pelvic pain and the GSS Brief, $r = .56$ 95% [.45, .64], $p < .001$, but a weaker positive relationship between GSS Brief and *MMH*, $r = .41$ [.28, .52], $p < .001$. Despite these correlations, all predictors demonstrated low multicollinearity (variance inflation factor <2) across all four years in regression models predicting pelvic pain outcome as a function of *MMH*, the GSS Brief, and baseline pelvic pain serving a covariate. Baseline pelvic pain decreased in predictive strength over time, while *MMH* increased in predictive strength. However, the GSS Brief did not predict pelvic pain outcome at any year, suggesting that *MMH* is a better predictor of outcome than questionnaire-based methods (see Table S4).

Discussion

Inadequate understanding of mechanisms underlying pain sensitivity, and how sensitivity conveys risk for developing chronic pain, remains a barrier to treating and preventing chronic pain conditions. QST is the most widely used method for systematically measuring

pain sensitivity [21,22,77]; however, traditional assays that measure single nociceptive modalities (e.g., thermal, pressure) have demonstrated inconsistent predictive power for pain outcome [15,31,80,89]. Likewise, the ability of dynamic QST paradigms assessing pain modulation, such as CPM and TS, to predict pain outcome have also been mixed [27,66,70,71]. Our results demonstrate that the utility of QST can be improved by measuring sensory hypersensitivity more broadly (i.e., including several disparate sensory modalities to evaluate MMH). This approach is aligned with the repeated observation that many functional pain syndromes additionally report increased sensitivity to environmental stimuli (e.g., lights, sounds, odors). Thus, dysfunction in global sensory processing may be more crucial to chronic pain risk than any nociceptive mechanism underlying hyperalgesia.

In a cohort of women with a range of chronic pelvic pain risk, we found that including both nociceptive and non-nociceptive (e.g., visual and auditory) assays identified that PC1, *MMH,* was a robust common denominator underlying sensory testing variability. Notably, baseline *MMH* predicted pelvic pain annually for four years even when accounting for baseline pelvic pain. *MMH* outperformed sensory sensitivity composite models and was a better predictor of outcome than a questionnaire-based method of assessing generalized sensory sensitivity. MMH, rather than solitary dysfunction in specific nociceptive modalities or pain modulation, appears to underlie evolution of pain vulnerability and likely plays a substantial role in the development of chronic pain conditions.

MMH: Nociceptive and Non-Nociceptive QST

QST studies often infer centralized or generalized mechanisms of pain sensitivity to explain observed hypersensitivity in chronic pain conditions [30,34,40,41,45,46,51,53,59,65]. Relationships between and within QST modalities supports the hypothesis that QST assays measure distinct mechanisms of pain sensitivity [39,47,55,61]. However, given that most studies relied on singular noxious modalities of QST, or combinatory approaches of select modalities (e.g., heat and pressure), they provide only a limited ability to evaluate generalized mechanisms of hypersensitivity in centralized pain conditions [13].

The current investigation improves upon these previous attempts by administering a broader panel of nociceptive sensory tests (PPTs, CPM, TS, cold pressor, bladder provocation) and non-nociceptive supraspinal tests (visual and auditory sensitivity). Like previous QST studies [39,47], a PCA of these 40 QST measures resulted in modality-specific components: *PPT S-R* [79] and *bladder hypersensitivity* [91]. In contrast, the largest source of underlying QST variability was *MMH*, a component that was not modality specific. Although previous studies have conjectured that centralized hypersensitivity (e.g., generalized sensory sensitivity, somatization, somatic symptoms disorders, sensory modulation disorder, etc.) [8,14,23,85] underlies chronic pain conditions, our results provide evidence of MMH being a broad construct that correlates with affective symptoms, somatic symptoms, genitourinary pain, menstrual pain, and overall pain and health. Given the consistent and robust correlation between *MMH* and these other factors crucially affecting chronic pain, we hypothesize neural regions underlying MMH, such as the insula and cingulate cortex [e.g., 4,45,64,83], contain critical circuits in functional pain syndromes.

PC1 (*MMH*) Predicts Pelvic Pain Outcome

Studies that have used various QST measures to predict long-term outcome have not generated uniform conclusions [e.g., 27,35,38,46,66,67,86,98,99]. In contrast, current pain intensity has consistently been associated with future pain experience [3,33,60,98]. This investigation may explain the equivocal findings for QST on future pain outcomes: risk for worse pain outcome is possibly not due to alterations in normal interpretation of specific nociceptive modalities, but rather MMH. When testing whether current pain (baseline pelvic pain), *MMH*, or nociceptive modality-specific components (PCs 2 and 3) best predicted future pelvic pain outcome, we found that current pain provided a diminishing degree of predictive power annually, while *MMH* provided an increasing degree of predictive power over time. Additionally, *MMH* was the only significant predictor of year four pelvic pain intensity. This pattern of results held consistent even when adjusting for population prevalence rates of dysmenorrhea, bladder pain syndrome, and other types of chronic pain (see Figure S1).

In contrast, sensory testing composites sporadically predicted pelvic pain outcome: a more sensitive bladder test and QST assessment predicted worse pelvic pain at years three and four, respectively, with baseline pelvic pain decreasing in predictive power annually. A similar pattern of results was observed when adjusting for population prevalence rates; however, baseline pelvic pain became an important predictor of year four pelvic pain (see Figure S1). When sensory testing was split into composite measures, current (baseline) pelvic pain was the best predictor of future pelvic pain, but longitudinal estimates became unstable.

Therefore, the modality-specific QST differences often observed in cross-sectional studies comparing pain patients to controls [e.g., 40,46] could reflect dynamic states of hypersensitivity. In contrast, the increased MMH in participants that develop worse pelvic pain suggest that a pervasive sensory processing mechanism is stable across time.

Strengths and Limitations

The multimodal sensory testing panel used here is one of the largest efforts to characterize MMH in individuals harboring variable degrees of risk for CPP and includes one of the longest follow-up periods of any previous QST pelvic pain study. The current investigation leveraged PCA that facilitated dimensionality reduction (from 40 to 3 variables) in a racially diverse sample enriched with at-risk individuals. However, some limitations may affect the generalizability of our results. The sample included a large number of college students. As a result, the sample was young (M=25, SD=6 years), and the vast majority were nulliparous (85% without a prior pregnancy). A strength of our study is the long-term follow-up, although there was some attrition. Prior studies of long-term pain had comparable attrition rates (50–80%), and attrition had a marginal impact on outcome [28,81]. Together, our analyses suggest that longitudinal data were missing at random and did not selectively depend on recruited participant groups, pelvic pain outcome, nor predictor variables of interest calculated either via sensory testing composites or PCA.

Given that comprehensive multimodal sensory testing is onerous on patients and staff, it remains challenging to validate these findings within large clinical populations. Although the longitudinal stability of *MMH* is unknown, it is encouraging that *MMH* derived from a one-day sensory testing panel predicted a single week of average pelvic pain four years later. Future work would be well served to establish the minimum battery of sensory tests needed to evaluate MMH. Thus, we envision that with further refinements of MMH testing, such as automated methods [e.g., 46], it may possible to validate a clinically oriented short protocol. Developing early predictive methods for long-term chronic pain risk are essential for preventing its deleterious effects. Because the goal of CRAMPP was to evaluate the role of menstrual pain and other nociceptive mechanisms in the development of chronic pelvic pain in an at-risk cohort, the follow-up questionnaires were specifically focused towards interrogating pelvic pain. Future studies should investigate the role of MMH on non-pelvic pain risk.

Conclusion

This analysis provided crucial evidence supporting MMH, a hypothesized construct underlying “centralized” mechanisms of pain sensitivity, and its predictive ability of worse pelvic pain outcome. Our study demonstrates that multimodal sensory testing improves the prediction of pain status or outcome over parsimonious unimodal approaches or questionnaire-based strategies. MMH exists on a continuum, and individuals that report increased sensory sensitivity or demonstrate hypersensitive QST responses are more vulnerable to worse future pain [8,38,66,89]. Neuroimaging paradigms have implicated the anterior insula and cingulate cortex as important for multimodal sensory integration and nociceptive appraisal [44,45,64]. Therefore, future work to abrogate the course of chronic pain would be well served to understand and target the neural mechanisms that underlie MMH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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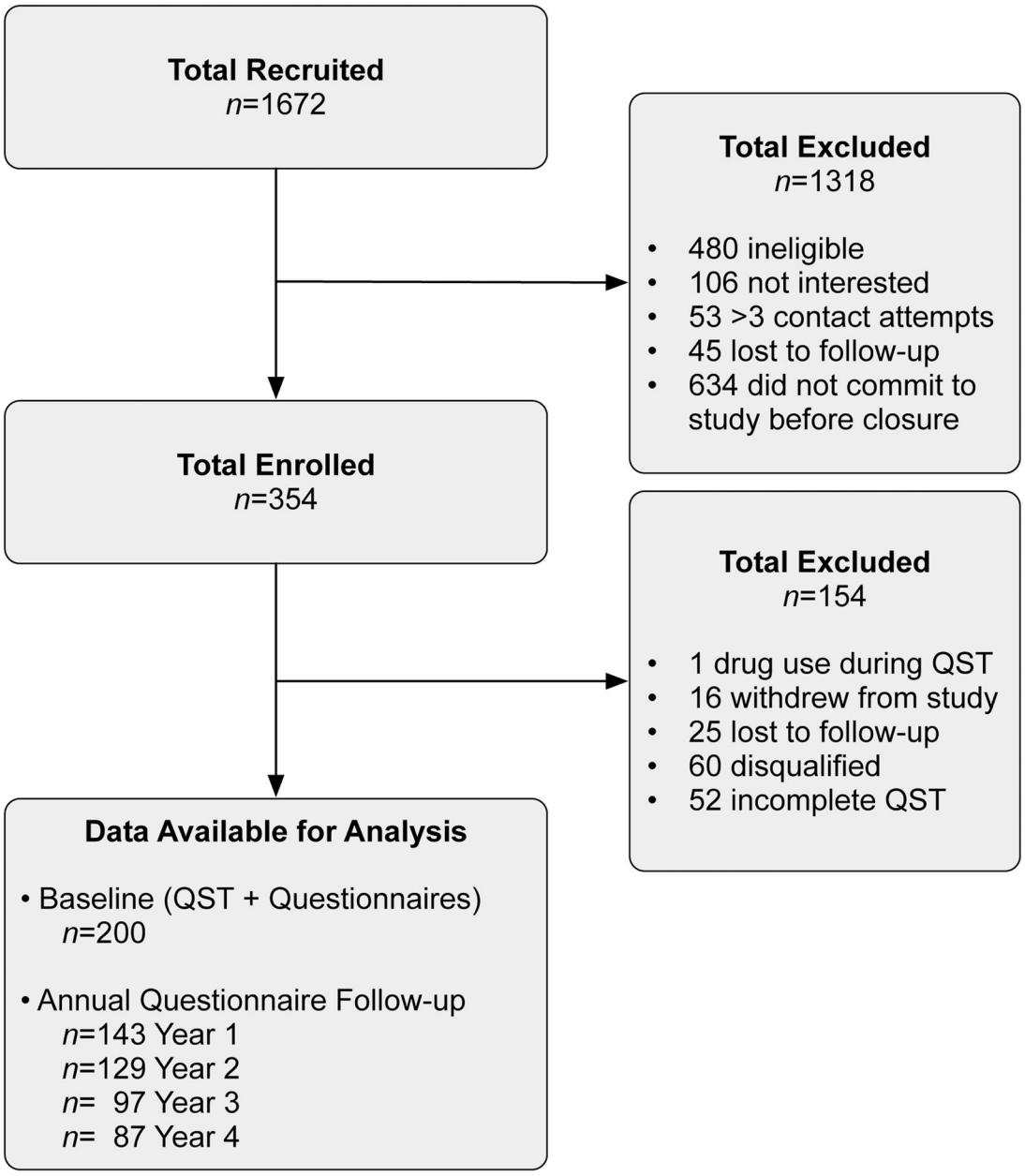

Figure 1.
Participant Recruitment and Enrollment Flowchart for CRAMPP.

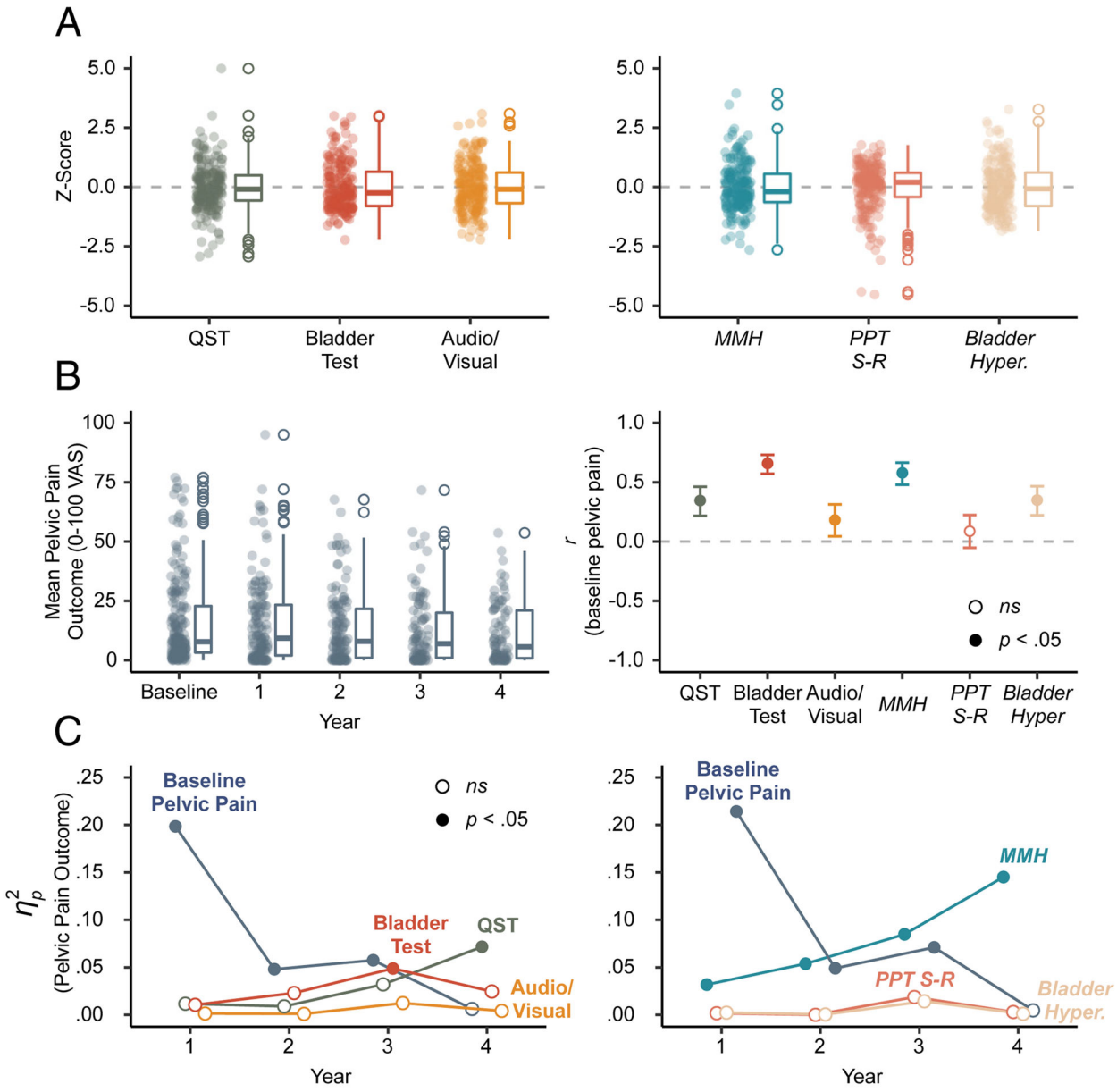

Figure 2. *MMH* provides better prediction of future pelvic pain.

A) Box plots of Z-scores for each sensory testing composite variable (*left*) and principal component (PC) used for regression modeling (*right*). B) Box plots of pelvic pain outcome across the baseline visit and annual questionnaires (*left*); Correlations between baseline pelvic pain and predictors (i.e., sensory testing composites and PCs). Error bars are 95% confidence intervals and all correlations were significant (filled circles) except *PPT S-R* (*right*). C) Explained variance (η_p^2) of pelvic pain outcome for each sensory testing composite (*left*) and PC (*right*) accounting for baseline pelvic pain. Significant predictors (filled circles) include baseline pelvic pain, bladder test, QST, and *MMH*. Italicized text labels refer to PCs. QST=quantitative sensory testing; *MMH*=multimodal hypersensitivity; *PPT-SR*=pressure

pain threshold stimulus-response (function); Hyper.=hypersensitivity; VAS=visual analog scale.

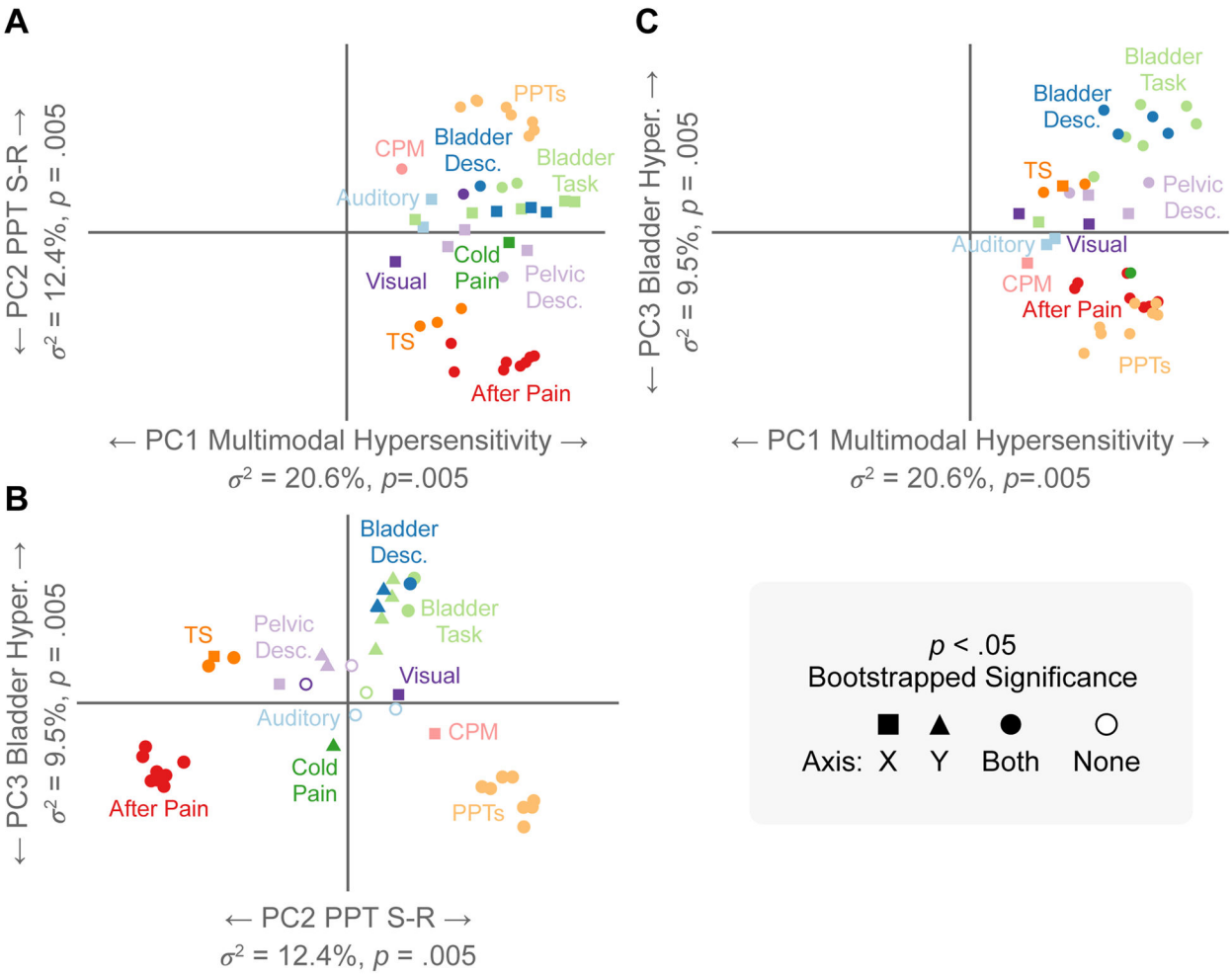

Figure 3. Factor Score Plots of Sensory Testing Variables.

Each measure's position denotes its relative loading/correlation with the orthogonal principal components (PCs) plotted across the x-y coordinate plane. Measures in close proximity within an axis plane depict positive relationships (concomitant sensitivity across proximal measures). Measures that are distant appear on opposite sides of the origin and depict negative relationships within an axis plane. A bootstrapping procedure quantified loading significance for each measure on each PC depicted with shapes. A) Within the x-axis plane (PC1), all measures load positively onto PC1 and are proximal, indicating positive relationships across all measures with PC1. B) Within the x-axis plane (PC2), PPTs and after-pain measures are distant from each other and are located on opposite sides of the origin. This indicates a negative relationship between PPTs and after-pain measures (this can also be seen across the y-axis in A). Within the y-axis plane (PC3), measures from the bladder task positively load onto PC3 and are distant/oppose the PPTs and after-pain measures. C) Loading patterns of PC1 (x-axis) and PC3 (y-axis). Bladder Task = pain and urgency measurements; Bladder Desc.= Bladder descriptors of Dull/Pressing/Prickling/Sharp pain; PC=Principal Component; PPTs=Pressure Pain Thresholds; CPM=Conditioned Pain Modulation; TS=Temporal Summation.

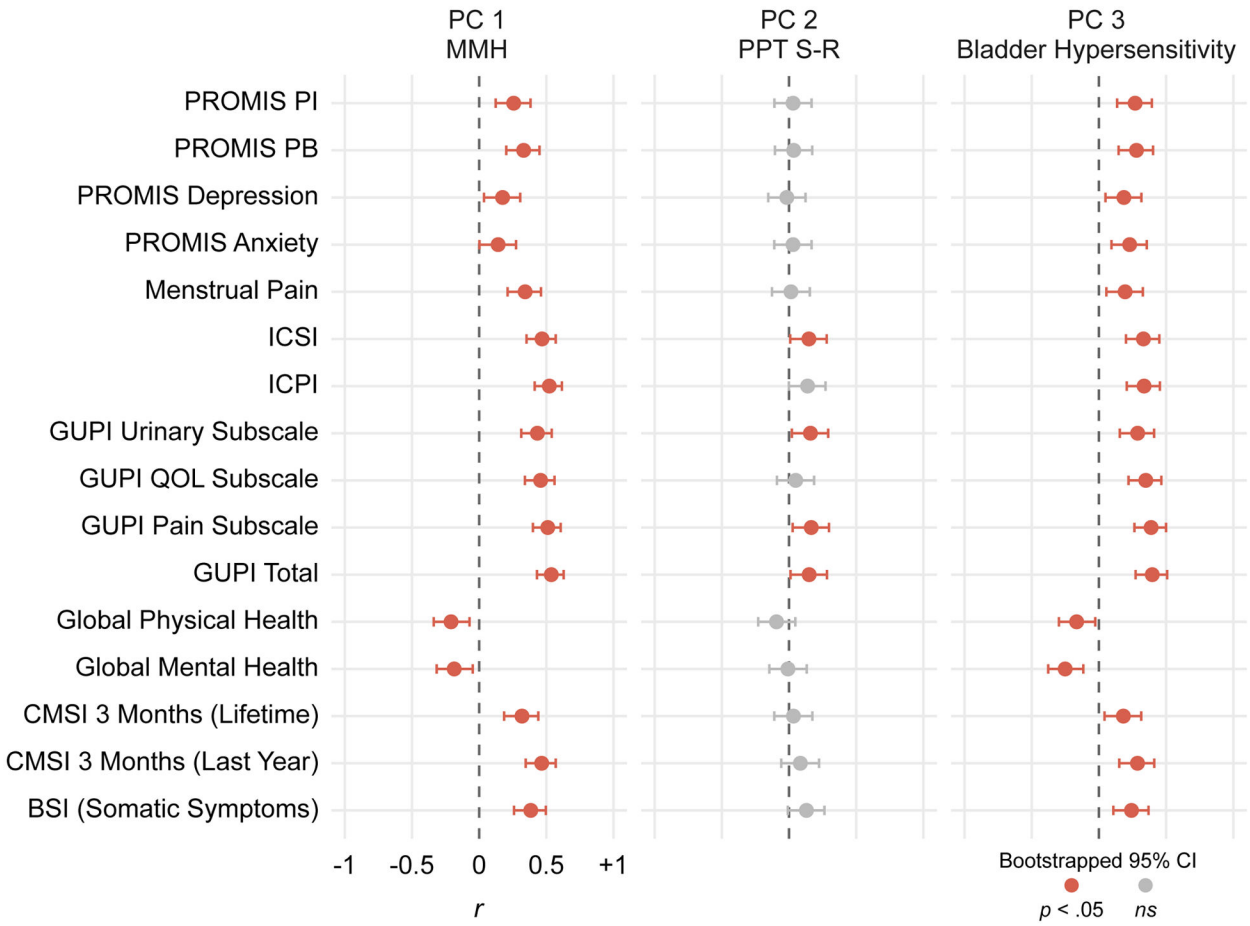

Figure 4. Correlations Between Principal Components (PCs) and Self-Report Questionnaires.

Each point depicts a Pearson's pairwise correlation between the participants' factor scores across the three PCs of interest and their responses to a self-report questionnaire. Error bars denote bootstrapped 95% confidence intervals; therefore, intervals crossing zero indicate non-significant correlations and are colored grey. Except for global mental/physical health, greater scores on self-report questionnaires denote worse symptoms/outcome. All MMH and bladder hypersensitivity correlations were significant and in the expected direction: greater hypersensitivity was associated with worse affective symptoms, somatic symptoms, genitourinary pain, menstrual pain, and overall pain and health. PROMIS=Patient Reported Outcomes Measurement Information System; PI=Pain Interference; PB=Pain Behavior; ICSI=Interstitial Cystitis Symptom Index; ICPI= Interstitial Cystitis Problem Index; GUPI=Genitourinary Pain Index; QOL=Quality of Life; CMSI=Complex Medical Symptoms Inventory; BSI=Brief Symptom Inventory.

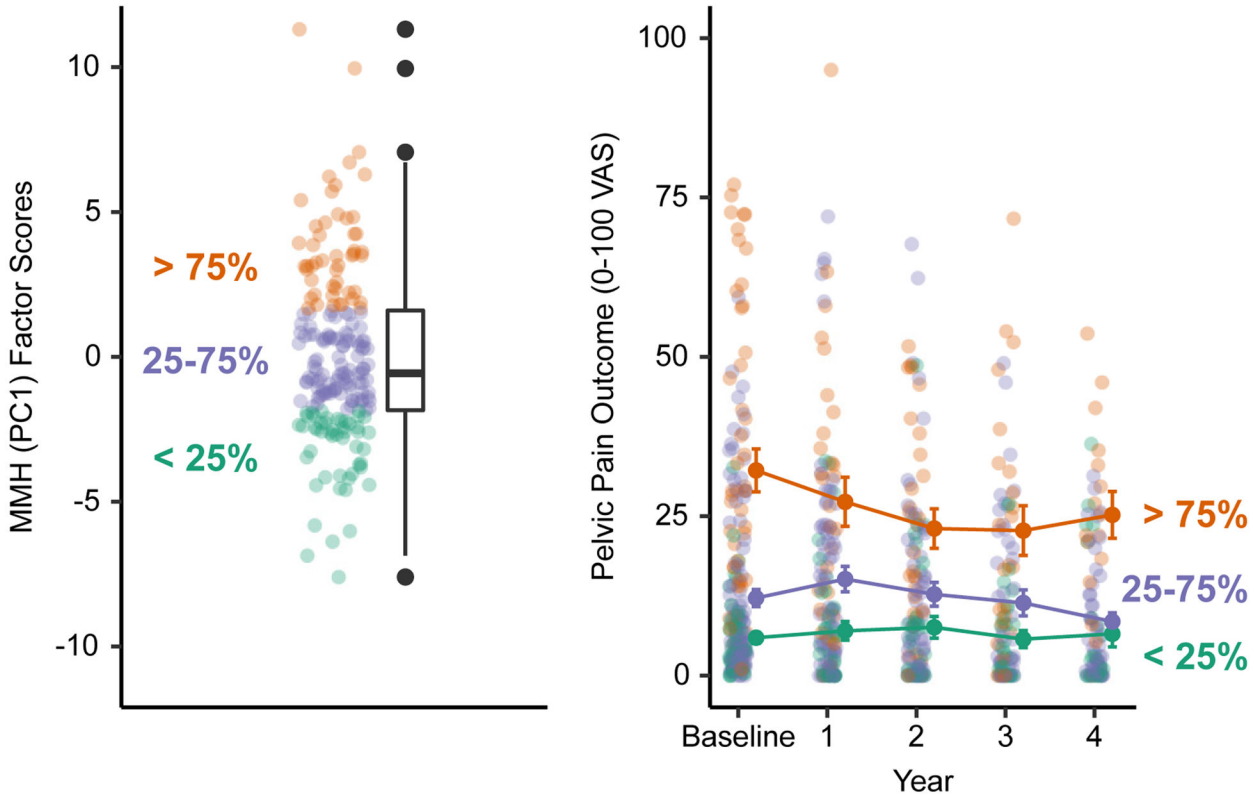

Figure 5. *MMH* (PC1) Outer-Quartile Participants Demonstrate Different Pelvic Pain Trajectories.

Participants were first differentiated based on whether they are inside or outside the inter-quartile range for baseline *MMH* (PC1) factor loadings (*left*). Participants with *MMH* (PC1) factor scores > 75% of the sample demonstrated worse pelvic pain outcome at baseline that persisted across the four-year follow-up period (*right*). Error bars are the standard error of the mean.

Table 1.

Participant Baseline Demographics.

Measure	***n* (%)**	***Mean* (*SD*)**	**Measure**	***n* (%)**
Race			**Pre-Existing conditions**	
White	121 (60.5%)		Ovarian Cysts	27 (14%)
Black or African American	32 (16%)		Lower Back Pain	21 (11%)
Asian	30 (15%)		Chronic Pelvic Pain	18 (9%)
Multiple	15 (7.5%)		Migraine Headaches	18 (9%)
Native American	1 (.5%)		Irritable Bowel Syndrome	16 (8%)
No Response	1 (.5%)		Bladder Pain Syndrome	13 (7%)
Ethnicity			Endometriosis	13 (7%)
Not Hispanic or Latino	176 (88%)		Chronic Constipation	6 (3%)
Hispanic or Latino	24 (12%)		Fibroids	5 (3%)
Groups			Inflammatory Bowel Disease	5 (3%)
Dysmenorrhea	132 (66%)		Kidney Stones	4 (2%)
Pain-Free Controls	30 (15%)		Fibromyalgia	3 (2%)
Chronic Pain	22 (11%)		Pelvic Inflammatory Disease	1 (1%)
Bladder Pain Syndrome	16 (8%)		Chronic Diarrhea	1 (1%)
Age (years)	200	24.9 (6.4)	Arthritis	1 (1%)
Height (inches)	196	64.6 (2.8)	**Parous**	
Weight (lbs.)	195	143 (30.1)	Ever Pregnant	29 (15%)
Body Mass Index (BMI)	195	24 (4.63)	1 or more deliveries	14 (7%)

Note. Percentages were calculated from the total sample size (n=200). Some participants had multiple diagnoses.

Table 2.

Descriptive Statistics for PPTs and Bladder Task of CRAMPP Participants.

QST Measure	*Mean*	*SD*	*Min*	*Max*
PPT (Newtons)				
Vaginal 12 o'clock	9.7	6.8	0.9	30.7
Vaginal 5 o'clock	9.0	5.6	0.4	31.0
Vaginal 6 o'clock	8.6	5.6	0.6	29.4
Vaginal 7 o'clock	7.2	4.9	0.8	30.1
Forehead	18.1	8.9	3.5	42.5
Hip	25.5	12.0	4.5	73.7
Knee	21.8	9.6	2.1	65.3
Shoulder	20.4	9.8	4.4	57.2
After-pain (baseline adjusted 0–10 NRS)				
Vaginal 12 o'clock	1.4	1.0	−4.0	6.0
Vaginal 5 o'clock	1.5	1.1	−3.0	6.5
Vaginal 6 o'clock	1.4	1.0	−3.0	7.0
Vaginal 7 o'clock	1.5	1.1	−3.5	7.0
Forehead	1.2	0.6	0.0	5.0
Hip	1.3	0.7	−0.5	5.5
Knee	1.2	0.6	−0.5	3.5
Shoulder	1.2	0.6	−3.0	4.5
Bladder Task (0–100 VAS)				
BL Pain	5.1	10.7	0	57
FS Pain	8.4	13.4	0	66
FU Pain	16.2	19.9	0	100
MT Pain	30.7	29.5	0	93
FS Urgency	21.7	14.1	0	67
FU Urgency	48.8	16.2	2	100
MT Urgency	83.4	12.9	6	100
Bladder Descriptors (0–100 VAS)				
Dull	27.3	28.1	0	90
Pressing	48.2	32.0	0	100
Prickling	13.9	20.6	0	87
Sharp	20.3	25.6	0	98
Pelvic Descriptors (0–10 NRS)				
Dull	1.4	1.7	0	9
Pressing	3.3	2.3	0	10
Prickling	0.6	1.5	0	8
Sharp	2.0	1.9	0	8

Note. After-pain ratings were adjusted by subtracting the baseline pain ratings prior to PPT testing. Therefore, negative values are possible when PPT reduced after-pain ratings below the baseline. PPT=Pressure Pain Threshold; BL=Baseline; FS=First Sensation; FU=First Urge; MT=Maximum Tolerance; NRS=numeric rating scale; VAS=visual analog scale.

Table 3.

Additional Multimodal Sensory Testing Descriptive Statistics (Cold Pain, CPM, TS, and Visual/Auditory Stimulation) of CRAMPP Participants.

Measure	*Mean*	*SD*	*Min*	*Max*
Cold Pain (0–10 NRS)				
Rating	5.49	2.34	0	10
Residuals	−0.1	2.3	−5.7	4.5
CPM				
Left Knee (Newtons)	6.7	9.1	−10.8	47.2
Temporal Summation				
Max Trial	9.5	1.6	2	10
Mean Pain (0–10 NRS)	2.2	1.3	−0.5	5.3
Slope	0.2	0.4	−0.3	3.0
Visual Unpleasantness				
Mean (0–20 GBS)	8.1	3.9	0.0	19.6
Slope	0.6	0.7	−1.5	3.0
Auditory Unpleasantness				
Mean (0–20 GBS)	6.4	2.5	1.2	13.6
Slope	1.9	0.8	−1.3	4.0

Note. Cold pain residuals, not ratings, were used in the principal component analysis. CPM=conditioned pain modulation; NRS=numeric rating scale; GBS=Gracely Box Scale.

Table 4.

Regression Models of Pelvic Pain Outcome for Summed Z-Score Sensory Testing Composites.

Year	Parameter	*b*	*SE*	β	η_p^2	*SS*	*MSE*	*F*	*p*
1	Intercept	16.3	1.2		0.58	37298	194	191.9	< .001
	Baseline Pelvic Pain	0.5	0.1	0.51	0.20	6641		34.2	< .001
	QST	0.1	0.1	0.10	0.01	318		1.6	0.20
	Bladder Test	0.3	0.2	0.11	0.01	286		1.5	0.23
	Audio/Visual	0.2	0.5	0.03	0.00	37		0.2	0.66
2	Intercept	14.2	1.2		0.52	25407	186	135.8	< .001
	Baseline Pelvic Pain	0.2	0.1	0.26	0.05	1171		6.3	0.01
	QST	0.1	0.1	0.10	0.01	209		1.1	0.29
	Bladder Test	0.4	0.2	0.19	0.02	546		2.9	0.09
	Audio/Visual	0.2	0.5	0.03	0.00	23		0.1	0.72
3	Intercept	12.8	1.3		0.51	15380	160	95.2	< .001
	Baseline Pelvic Pain	0.2	0.1	0.27	0.06	907		5.6	0.02
	QST	0.2	0.1	0.17	0.03	493		3.0	0.08
	Bladder Test	0.5	0.2	0.26	0.05	762		4.7	0.03
	Audio/Visual	−0.6	0.5	−0.10	0.01	187		1.2	0.29
4	Intercept	11.7	1.2		0.52	11317	127	89.4	< .001
	Baseline Pelvic Pain	0.1	0.1	0.10	0.01	65		0.5	0.48
	QST	0.3	0.1	0.27	0.07	801		6.3	0.01
	Bladder Test	0.4	0.3	0.21	0.02	262		2.1	0.15
	Audio/Visual	0.3	0.5	0.06	0.00	43		0.3	0.56

Note. The *df* for each model were: Year 1 (1, 138), Year 2 (1, 124), Year 3 (1, 92), and Year 4 (1, 82).

Table 5.

Regression Models of Pelvic Pain Outcome for PCA-based Construct Models.

Year	Parameter	*b*	*SE*	β	η_p^2	*SS*	*MSE*	*F*	*p*
1	Intercept	16.3	1.2		0.59	37791	194	195.1	< .001
	Baseline Pelvic Pain	0.6	0.1	0.54	0.21	7287		37.6	< .001
	PC 1 - MMH	1.1	0.5	0.17	0.03	878		4.5	0.04
	PC 2 - PPT S-R	−0.3	0.6	−0.03	< .01	46		0.2	0.63
	PC 3 - Bladder Hyper.	−0.4	0.7	−0.04	< .01	61		0.3	0.57
2	Intercept	14.3	1.2		0.53	25600	186	137.4	< .001
	Baseline Pelvic Pain	0.3	0.1	0.27	0.05	1192		6.4	0.01
	PC 1 - MMH	1.4	0.5	0.25	0.05	1315		7.1	0.01
	PC 2 - PPT S-R	0.1	0.6	0.01	< .01	1		0.0	0.93
	PC 3 - Bladder Hyper.	0.2	0.7	0.02	< .01	10		0.1	0.82
3	Intercept	12.6	1.3		0.50	14737	160	91.9	< .001
	Baseline Pelvic Pain	0.3	0.1	0.31	0.07	1128		7.0	0.01
	PC 1 - MMH	1.6	0.6	0.31	0.08	1366		8.5	0.004
	PC 2 - PPT S-R	−0.7	0.6	−0.12	0.02	282		1.8	0.19
	PC 3 - Bladder Hyper.	0.8	0.7	0.11	0.01	213		1.3	0.25
4	Intercept	11.8	1.2		0.53	11506	127	90.8	< .001
	Baseline Pelvic Pain	0.1	0.1	0.09	< .01	49		0.4	0.54
	PC 1 - MMH	2.0	0.5	0.44	0.15	1763		13.9	< .001
	PC 2 - PPT S-R	−0.3	0.6	−0.05	< .01	31		0.2	0.62
	PC 3 - Bladder Hyper.	0.2	0.7	0.03	< .01	11		0.1	0.77

Note. The *df* for each model were: Year 1 (1, 138), Year 2 (1, 124), Year 3 (1, 92), and Year 4 (1, 82). MMH=multimodal hypersensitivity; PPT S-R=pressure pain threshold stimulus-response; CI=confidence interval